Prostate

Introduction

Men and women have the same micturition reflex arcs in the spinal cord, the same sensation of the need to void, and the same possible urinary issues listed in the last lesson. The point isn't that they are all equally as likely in men and women; it's that they are possible in both sexes. But guys have a special appendage. And no, not the one that makes the urethra longer (though we do end this lesson with erectile dysfunction pharmacology). The extra male appendage, as it relates to the bladder and urethra, is the **prostate**. The emphasis is going to be on the prostate, benign prostatic hyperplasia, prostate cancer, prostatitis, and the management of obstructive urinary symptoms caused by benign prostatic hyperplasia.

Prostate Anatomy

The **prostate** is the largest accessory sex gland, and is about the size of a walnut. It is often discussed in the context of reproduction. This is because its purpose is to secrete a clear, slightly alkaline fluid that helps form semen. The ejaculatory ducts flow through it, and it is, indeed, a reproductive organ. But when the prostate goes awry, it isn't reproduction that suffers—rather, its proximity to the urethra causes urinary symptoms.

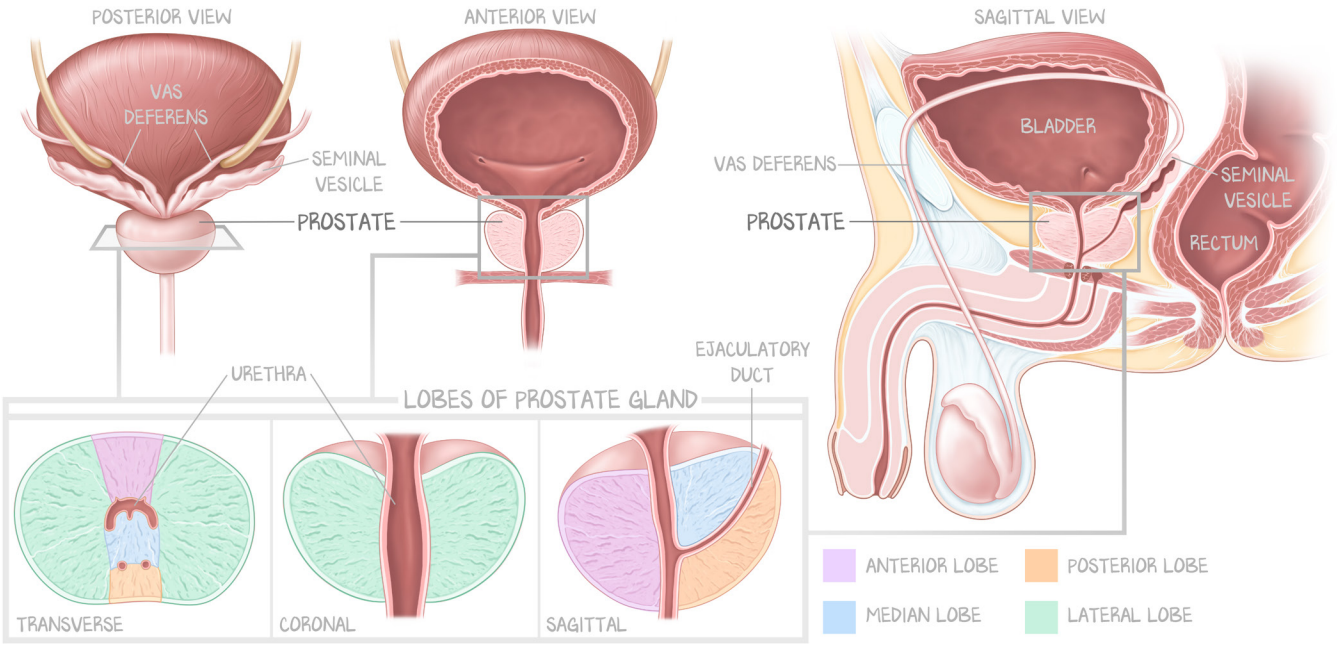


Figure 3.1: Prostate Anatomy
Showing a posterior, anterior, and sagittal view of the prostate gland. It then demonstrates the lobes of the prostate.

From an anatomic standpoint, **lobes** are generated mostly by the tubes that run through the prostate. There are five lobes. The anterior lobe is in the front. There are two lateral lobes, one on either side. And the "back" of the prostate is separated into a median and a posterior lobe. The "front, back, and sides" are in relation to the urethra, which runs through the prostate. Anterior to the urethra is the anterior lobe. Lateral to the plane of the urethra are the lateral lobes. And posterior to the urethra are the median (closest to the urethra), then the posterior (farthest from the urethra) lobes . The median lobe and posterior lobe are continuous, except where the ejaculatory ducts run through the prostate. The plane the ejaculatory ducts make between one another defines the an artificial boundary of the median and posterior lobes. This made sense when the only consideration was prostate cancer. Prostate cancer forms only in the posterior lobe.

When we discuss benign prostatic hypertrophy, the lobes don't work. Instead, we use **zones**. There are four—central, transitional, peripheral, and fibromuscular. The **transitional zone** is the zone immediately around the urethra. There is a small region posterior to the urethra, then it wraps and extends anteriorly. The **central zone** houses the seminal vesicles. It is posterior to the transitional zone, and sweeps up laterally to the plane of the urethra. The **peripheral zone** envelopes the central zone, and rises to just past the plane of the urethra on the lateral sides. The peripheral zone is at risk for malignant transformation—prostate cancer. Anterior to the transitional zone is the **fibromuscular stroma**. It sits between the transitional zone and the capsule.

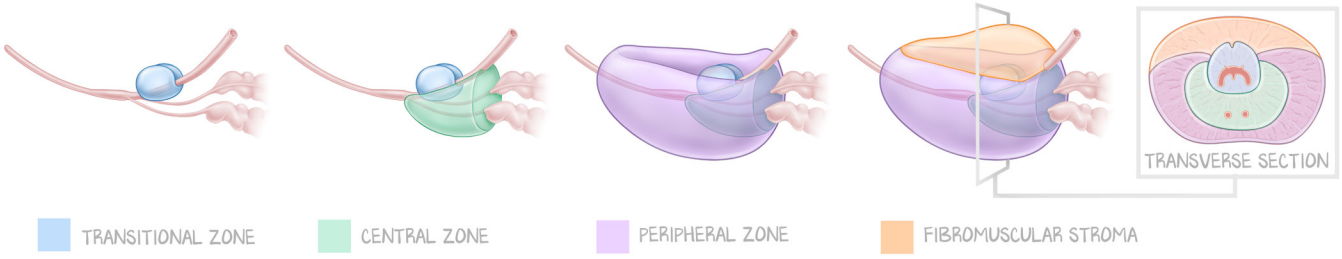


Figure 3.2: Zones of the Prostate
The innermost zone is the transitional zone, which surrounds the urethra. Then around that zone wraps the central zone, through which the ejaculatory ducts will run. Around the central and some of the transitional zone wraps the peripheral zone. The anterior of the prostate is capped by a fibromuscular stroma that sits atop the anterior portion of the transitional zone and peripheral zone.

Prostate Physiology

The prostate's main purpose is the alkalinization of semen, and the prostate gland contributes about 25% of the semen volume. Sperm are acid sensitive, so the alkalinity neutralizes the normal protective acidity of the vagina. That's all reproduction-level discussion. We'll come back to that in the Reproduction series. Here, we want to engage the prostate in relation to the urinary system and cancer.

The prostate has two other roles pertinent to our discussion now—secretion of prostate-specific, antigen and contraction against the urethra.

Contraction. During ejaculation, forceful contractions force the semen down and out of the urethra. This requires relaxation of the lower urethral sphincter. But in order to ensure the unilateral directionality DOWN the urethra and not back up into the bladder, the **prostate contracts around the urethra**. The internal urethral sphincter contracts through α_1 receptor stimulation. The prostate around the urethra, the **transitional zone**, also contracts around the urethra through α_1 receptors.

PSA synthesis. The prostate glandular cells make prostatic fluid for semen. Into that fluid they secrete **prostate-specific antigen (PSA)**. PSA is a product that healthy prostate cells secrete, and is a protein product that malignant prostate cells can secrete. The cells that make most of the prostatic secretions are in the **peripheral zone**. The peripheral zone is where most prostate cancer occurs. There is therefore a very logical conclusion—prostate cancers make PSA. That logical conclusion derailed cancer screening for decades. The PSA was previously used as a screening tool for prostate cancer. The PSA is now no longer recommended as a screening tool (false-positive rates led to unnecessary prostate biopsies that were negative for malignancy but ended up in fistulas and erectile dysfunction, AND it turns out there was no mortality benefit for those found to have cancer). But what it can be used for is **tracking remission** or **relapse** of prostate cancer. If the prostate cancer is making PSA, the PSA will start high. If the entire prostate is removed, cancer included, then no PSA should be made, and the PSA will fall to undetectable levels. If the PSA begins to rise without a prostate, it means the cancer is back.

Prostate cell growth. Testosterone is a steroid hormone and acts as a growth factor. Testosterone enters both stromal cells and glandular cells of the prostate, activates cytoplasmic receptors, translocates to the nucleus, and induces proliferation. **Dihydrotestosterone (DHT)** is 30 times more potent than testosterone at inducing proliferation of stromal and epithelial cells. Testosterone, in addition to acting as a growth factor in stromal cells, is also converted to DHT by stromal cells via the enzyme **5α-reductase**. DHT is also a steroid hormone and freely diffuses through plasma membranes, activating proliferation of stromal cells and epithelial cells.

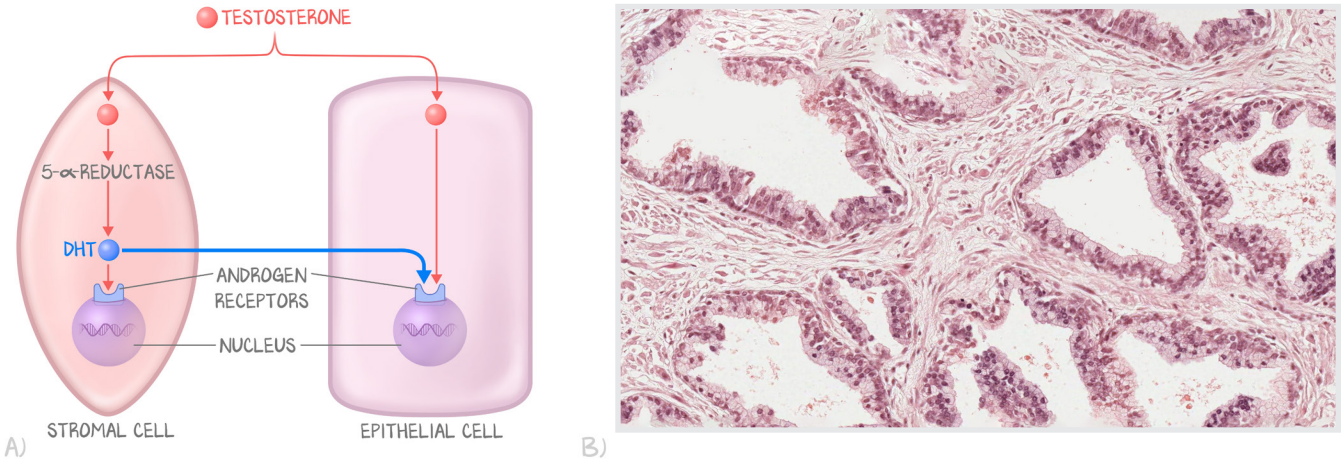


Figure 3.3: Cells of the Prostate
(a) Physiology and relationship between the epithelial cells of the glands and the stromal cells in regard to testosterone. (b) The epithelial cells are the cells lining the glands (the white space), and the stromal cells are the cells of the pink amorphous stuff between glands. Glandular cells are the epithelium that lines the glands.

BPH

Benign prostatic hyperplasia is caused by proliferation of healthy cells, and is so **hyperplasia**, not hypertrophy. The disease got its original name, benign prostatic hypertrophy, because the prostate gland got bigger. There was indeed hypertrophy of the organ called the prostate (the pathologic definition of glandular hypertrophy is an increased weight). At the cellular level, however, the more accurate diagnosis is hyperplasia. This is typically a disease of old men. The prostate responds to DHT, a more potent androgen hormone than testosterone, with growth. Testosterone is converted to DHT by 5α-reductase. The areas that **can proliferate**, **do proliferate**. These cells are in the **transitional zone**. Both stromal cells and glandular epithelial cells proliferate. The transitional zone hyperplasia **grows into the urethra** (which, as a hollow tube, offers little resistance). When that happens, the urethra becomes obstructed. Only a little at first, but then, left unchecked, could get obstructed a lot.

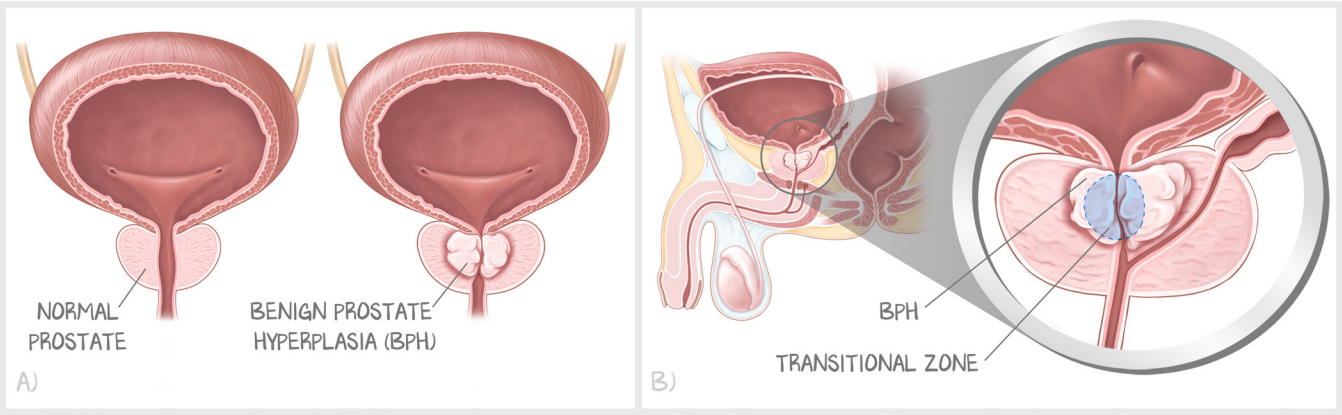


Figure 3.4: Benign Prostate Hyperplasia
(a) Pathophysiologic outcome of an enlarged prostate. (b) Anatomy and zone of its growth.

Patients present with difficulty starting their urine stream (called **hesitancy**), often needing to strain to initiate the urine stream, a sense of **incomplete voiding**, and **post-void dribbling**. The bladder, a muscle, must contract against increased resistance (a narrowed urethral lumen) and so may hypertrophy. This presentation is a result of the prostate acting as an unregulated and unintended urethral sphincter. Generating enough detrusor force (large-volume bladder and increased abdominal pressure) overcomes the "sphincter," and urine flow starts. But unlike the sphincters themselves, where initiation of voiding facilitates the PMC to keep the stream going by inhibiting both sphincters, voiding in BPH cannot "inhibit the prostate"—it is overgrown and obstructing.

A diagnosis can be made on symptoms alone and response to medical intervention. The rectal exam will show a **single rubbery nodule**. If the prostate is resected, you will see **well-demarcated nodules** in the **center of the prostate**. Microscopically, there is glandular and stromal hyperplasia. BPH is **never malignant** and hyperplasia of the prostate does not predispose to malignant transformation. Only perform a biopsy if the suspected diagnosis is prostate cancer.

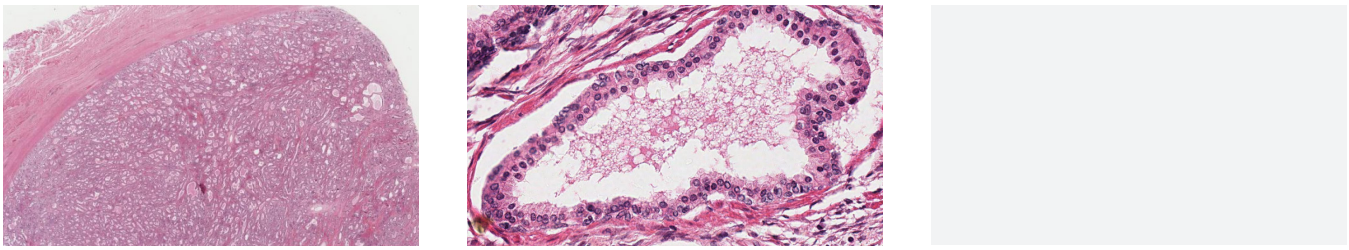


Figure 3.5: BPH Histology
Nodular prostatic hyperplasia. (a) Well-defined nodules of benign prostatic hyperplasia compress the urethra into a slit-like lumen. (b) A microscopic view of a whole mount of the prostate shows nodules of hyperplastic glands on both sides of the urethra. (c) Under high power, the characteristic dual cell population: the inner columnar and outer flattened basal cell can be seen.

Treatment for BPH can involve surgery (TURP, trans-urethral resection of the prostate), or it can be managed with medications. Most cases of BPH do not need surgery. The goal is to dilate the urethra and prevent proliferation of prostatic cells.

The **α_1 receptor antagonists** block the contraction of smooth muscle activated by α_1 receptors and **dilate the urethra**. Both the internal urethral sphincter and the prostate of the transitional zone have the ability to contract on the urethra via α_1 receptor stimulation. The α_1 receptor antagonists therefore cause dilation of the urethra, which results in **immediate symptom relief**—it is easier to pee with reduced resistance in the urethra. While these medications are not used as blood pressure treatment, they are α_1 blockers, and can cause **orthostatic hypotension**. Newer α_1 blockers have reduced risk of orthostatic hypotension. The most "urospecific" is **tamsulosin**.

EXAMPLES	SIDE EFFECT	CONTRAINDICATIONS	INDICATIONS
Gen 1: Prazosin Terazosin Doxazosin	Reflex tachycardia Orthostatic hypotension Delayed erection Floppy iris	Orthostatic hypotension	BPH urinary symptom improvement
Gen 2, Gen 3: Silodosin Alfuzosin Tamsulosin	Delayed ejaculation Floppy iris syndrome	Orthostatic hypotension	BPH urinary symptom improvement

Table 3.1: α Antagonists for BPH

5α-reductase inhibitors prevent the conversion of testosterone to DHT. No DHT means no nuclear transcription factor translocation, means no proliferation. This is indicated in all men who have BPH. Because it impacts nuclear transcription factors and cell proliferation, this will take a **long time to have an effect**. It is a chronic medication that will not relieve symptoms today, or even this week. **Finasteride** is the prototypical 5α-reductase inhibitor. The **side effect** is the same side effect as having too little testosterone—sexual dysfunction and lack of energy. Finasteride topical is also used for regrowing hair in male pattern baldness, so guys might see some of their hair come back. However, **reduced libido**, **impotence**, and **gynecomastia** prevent men from wanting to take the medication, especially when there is no perceived immediate benefit. Gynecomastia is caused when excess testosterone (that would have normally been converted to DHT) is shunted to **estrogen**.

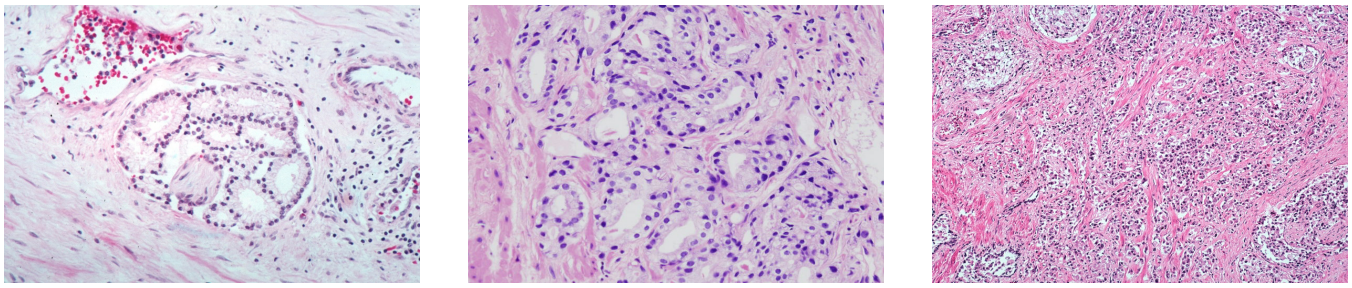
In addition, the 5α-reductase inhibitor can be **absorbed through the skin**, and is a **teratogen**, so should not be handled by women who are pregnant or will become pregnant.

EXAMPLES	SIDE EFFECTS	CONTRAINDICATIONS	INDICATIONS	NOTES
Dutasteride Finasteride	Hair growth Teratogen Reduced libido Impotence Gynecomastia	Women (hair growth) Pregnancy planned or desired	BPH enlargement	Finasteride 1 mg is for hair regrowth Finasteride 5 mg is for BPH

Table 3.2: 5α-Reductase Inhibitors for BPH

Prostate Cancer

Prostate cancer is the **most common cancer in men**. However, it has the lowest mortality. The saying goes, "*you die with prostate cancer, not from it.*" This is why we have stopped screening with PSAs. What happened was that men without cancer were getting biopsies that led to erectile dysfunction or vesiculo-rectal fistulas (high morbidity), AND those who were diagnosed had a significant lead-time bias—they weren't living longer, they were just living longer knowing they had prostate cancer because it got diagnosed sooner. This isn't a judgement of YOUR prostate cancer—some individuals did benefit. This is a judgement of the population's prostate cancer. The few people who benefited were out of all proportion to the many who suffered from the screening process. If you were not aware of PSA screening prior to doing this program, the repetition about the PSA is likely annoying—you got it already, right? But because PSA screening is so pervasive in clinical medicine, despite overwhelming recommendations to stop doing it, this lesson serves as a . . . get ready for it . . . public service announcement (PSA) on PSA.



(a) (b) (c)

Figure 3.6: Prostate Cancer Histology
a) Low-grade prostate cancer (Gleason score 1 + 1 = 2) consisting of back-to-back uniform-sized malignant glands. Glands contain eosinophilic intraluminal prostatic crystalloids, a feature more commonly seen in cancer than in benign glands, and more frequently seen in lower-grade than higher-grade prostate cancer. b) Needle biopsy of the prostate with variably sized, more widely dispersed glands of moderately differentiated adenocarcinoma (Gleason score 3 + 3 = 6). c) Undifferentiated adenocarcinoma (Gleason score 5 + 5 = 10) composed of sheets of malignant cells.

Prostate cancer is a **malignant growth** of the **peripheral zone** (the back, posterior, outside of the prostate). Prostate cancer is sensitive to androgen stimulation—the cancer grows from androgen stimulation just as the rest of the prostate does. Because it is growing off the back of the prostate, it usually **does not** cause urinary symptoms. It is an indolent tumor, with a slow doubling time. Digital rectal exam reveals a **firm**, **fixed**, **large**, **hard**, and **irregular nodule**.

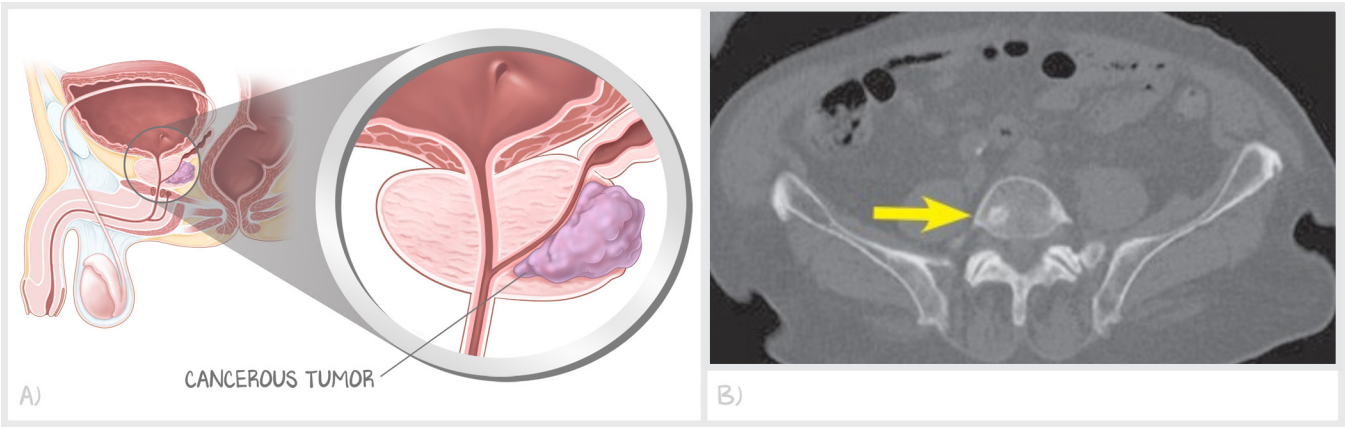


Figure 3.7: Prostate Cancer
(a) The prostate cancer occurs in the peripheral zone, often in the posterior lobe. This illustration shows the prostate cancer growing posteriorly away from the urethra and towards the rectum. (b) Prostate cancer often is asymptomatic until it metastasizes. A favorite metastatic site is the bone of the spine, demonstrated in this MRI.

Diagnosis is made by **transrectal ultrasound with biopsies**. These biopsies will allow you to calculate the Gleason score. Of 10 samples, you take the two that scored the highest for cancer, rank them on a scale of 1–5, then add those scores together. The higher the score, the more poorly differentiated the tumor, and the worse survival and response to therapy is. Separately, you will stage the patient with imaging. **Prostate cancer goes to bone.**

Treatments are variable. Radiation and chemo can get target large lesions causing symptoms. Prostatectomy can remove the source of the cancer. But it is often **orchiectomy** that is recommended. Since the cancer grows in response to DHT, and DHT comes from testosterone, which is made by the testes, removing the testes removes the growth source of the cancer. This obviously has an impact on sexual function and libido. Other medications that turn off the HPA axis (more on this in the Endocrine module), such as LHRH agonists or estrogens, can spare the man his testicles, but have similar side effects as orchiectomy.

Establish a **baseline PSA** and **trend/track the PSA over time**. Successful treatment will see the PSA fall. Remission will show the PSA remain negative. Failure or recurrence is when the PSA beings to rise. **DO NOT use the PSA for initial diagnosis or screening**. Do use it to track changes over time.

Prostatitis

Acute prostatitis is often a bacterial infection. In older men, it is the UTI bugs like *E. coli*, *Klebsiella*, and *Proteus*. In younger, sexually active men, prostatitis is more of an STI (**gonorrhea**, **chlamydia**). Either way there is translocation of bacteria in the urethra up into the prostate. These require antibiotics.

Prostatitis will present with **lower back pain** (referred pain), **fever**, and an **exquisitely tender prostate**. The prostate may be described as boggy. Once you make the diagnosis, never touch the prostate again, as all you will do is translocate bacteria into the bloodstream. The prostatic secretions, if expressed, will have **> 9 neutrophils** per high-powered field, though organisms may not be expressed. The **urinalysis** will look like a UTI. The **presentation** may look like a UTI (urgency, frequency, dysuria). But the tender prostate tells you otherwise.

Erectile Dysfunction

Erectile dysfunction doesn't really have anything to do with the urethra or prostate, but doesn't have anywhere else to live in the Basic Science course. Tadalafil ("Tada! Lafil") crosses the gap by providing erectile dysfunction support and also is used to treat BPH. Erectile dysfunction may be psychiatric or organic. Organic disease comes from dysfunctional nervous innervation (**p**arasympathetics induce erection, "**p**oint"; **s**ympathetics induce emission, "**s**queeze"; **s**omatic nerves ejaculate, "**s**hoot") or from diseased blood vessels (atherosclerosis from hypertension, diabetes). Erectile dysfunction may be a consequence of medication side effect (**β-blockers** or **SSRI**s).

To achieve and sustain an erection, there must be more blood in through the arteries than out through the veins. We discuss erectile dysfunction as a disease process in the clinical sciences. This brief review is of the nitric oxide pathway and on the medications that influence that pathway—the medications that open the arteries to make sure more blood flows in.

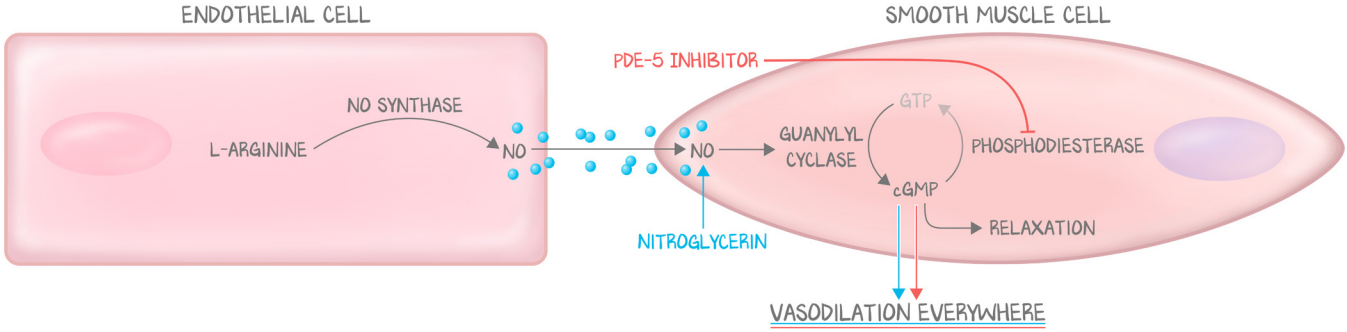


Figure 3.8: PDE-5 Inhibitor Mechanism of Action
Nitrates become nitric oxide. Endothelial cells release nitric oxide. Nitric oxide induces vasodilation. It does that by stimulating guanylyl cyclase to make cGMP from GTP. cGMP induces relaxation. Phosphodiesterase turns off cGMP to GTP.

Parasympathetic stimulation of the vascular endothelial cells releases nitric oxide. Nitric oxide diffuses across the endothelial cell into the smooth muscle cells. There, **nitric oxide (NO) activates guanylyl cyclase**. Regardless of where the NO comes from, guanylyl cyclase turns GTP into **cGMP**. cGMP is then responsible for **smooth muscle relaxation**. That's vasodilation.

Nitric oxide is normally produced from the **endothelial cells** (shown on the top of the image) via **NO synthase**, liberating NO from arginine. **Phosphodiesterase** reverts the active, vasodilating cGMP back into GTP. The phosphodiesterase **type is dependent** on the location of the smooth muscle cell. Inhibiting **PDE-5** results in smooth muscle relaxation in arteries. Other PDE types have nothing to do with vasculature. The phosphodiesterase type 5 inhibitors lead to vasodilation of the arteries of the penis. More flow in and therefore an erection. But there isn't a PDE-5 for the arteries of the penis, there are PDE-5s for all arteries everywhere, leading to side effects. Vasodilation everywhere leads to **hypotension**.

Nitrates are used for their antianginal properties. Nitroglycerin is used as an acute symptom reducer. Other nitrates are used as anti-hypertensives. Nitrates become nitric oxide and stimulate guanylyl cyclase to make cGMP. If we are adding nitric oxide to every blood vessel, then add on a phosphodiesterase inhibitor, the cumulative effect is vasodilation everywhere. This is why there is a risk of an unsafe drop in blood pressure, and why men taking nitrates should not use PDE-5 inhibitors. Also know that these drugs cause **blue-green color blindness**. **Tadalafil** has the longest duration, the greatest selectivity for PDE-5 only, and also has α_1 blocking effects.

EXAMPLES	SIDE EFFECT	CONTRAINDICATIONS	INDICATIONS	NOTES
Sildenafil Tadalafil	Priapism Necrotic penis (rare)	Men who take nitrates (severe hypotension)	Organic erectile dysfunction	Sildenafil 30 minutes prior Tadalafil every day, helps with BPH

Table 3.3: Prostate Diseases

DISEASE	CHARACTER
Benign Prostatic Hyperplasia	Histologically demonstrates a **double cell layer** and is a normal consequence of aging Presents as a **rubbery nodular mass** in the **transitional zone**, leading to **urinary tract obstruction** Urinary symptoms are dribbling, difficulty initiating urinary stream, and incomplete voiding Estrogens increase DHT receptors, while **DHT** stimulates growth Relieve urinary symptoms with α-blockers, shrink prostate with 5α-reductase inhibitors
Adenocarcinoma of Prostate	Histologically demonstrates a **single cell layer** duct Presents as a **discrete firm mass** in the **peripheral zone**, may lead to heme occult blood in stool Causes a **PSA** level **greater than 10** (do not rely only on this for diagnosis) Must be able to interpret **Gleason score** (2 = lowest, benign, 10 = highest, malignant) Growth is induced by **DHT** (removing source of testosterone [castration]) is recommended Alternatively, can use pharmacological castration with leuprolide Commonly spreads to the **spine** as a metastasis
Prostatitis	Inflammation of the prostate accompanying an ascending infection of the urethra Common organisms are gut flora such as ***E. coli*** or ***Enterococcus*** Pyogenic prostatitis = Bacterial infection = > 9 neutrophils per high-power field Nonbacterial prostatitis = Viral infection = lymphocytes and macrophages

Table 3.4: Prostate Diseases

DISEASE	EPITHELIAL LAYER	PSA/PAP	FEEL	ZONE	ANDROGENS
BPH	Double cell layer	Elevated < 10	Rubbery, nodular	Periurethral, transitional	Elevated estrogen pathogenic
Adenocarcinoma	Single cell layer	Elevated > 10	Discrete firm masses	Peripheral	Elevated estrogen protective

Table 3.5: BPH vs. Adenocarcinoma